

**Official title: A Tolerance Clinical Study on Aerosol Inhalation of Mesenchymal Stem Cells Exosomes in Healthy Volunteers**

**NCT number: NCT04313647**

**Document date: April 13<sup>th</sup>, 2020**

## **Informed Consent**

Dear volunteers (hereinafter referred to as subjects):

We sincerely invite you to participate in A Tolerance Clinical Study on Aerosol Inhalation of Mesenchymal Stem Cells Exosomes in Healthy Volunteers.

Please read the following as carefully as possible before you decide whether to participate in this study. It can help you understand the research, the procedure, and duration of the study, the possible benefits, risks, and adverse reactions of participating in the study. You could also discuss with your relatives and friends, or consult your doctor to help you make a decision. This informed consent is in duplicate; the investigator and you will each keep a copy after signing.

**Protocol Title:** A Tolerance Clinical Study on Aerosol Inhalation of Mesenchymal Stem Cells Exosomes in Healthy Volunteers

**Location:** Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

### **1. Study purpose**

Recruit healthy adults as participants. Every subject inhale different doses of the exosomes derived from allogenic adipose mesenchymal stem cells (MSCs-Exo), starting from the initial small dose. This clinical study

will be performed to evaluate the safety and tolerance of aerosol inhalation of MSCs-Exo in healthy volunteers, and to provide the reference basis for formulating the clinical treatment dose range for the follow-up clinical research on the treatment of severe pulmonary diseases.

## **2. Intervention**

Exosomes derived from allogenic adipose mesenchymal stem cells (MSCs-Exo)

## **3. Target population**

Healthy volunteers aged 19-45, regardless of gender.

## **4. Study background**

Exosomes are naturally occurring nanosized vesicles and comprised of natural lipid bilayers with an abundance of adhesive proteins that readily interact with cellular membranes. These vesicles contain cytokines growth factors, signaling lipids, mRNAs, and regulatory miRNAs. Exosomes are involved in cell-to-cell communication, cell signaling, and altering cell or tissue metabolism at short or long distances in the body, and influencing tissue responses to injury, infection, and disease.

Experimental studies have demonstrated that mesenchymal stem cells (MSCs) or their exosomes (MSCs-Exo) significantly reduced lung inflammation and pathological impairment resulting from different types of lung injury. Besides, macrophage phagocytosis, bacterial clearance, and prognosis were improved. MSCs-Exo likely has a similar therapeutic effect

on inoculation pneumonia as MSCs themselves.

Previous studies have found that MSCs-Exo has no irritation to blood vessels, muscles, and no hemolysis and skin allergy were caused by MSCs-Exo. After intranasal administration of MSCs-Exo, no abnormality was found in the heart, liver, spleen, lung, and kidney of mice. These results indicated that MSCs-Exo has great safety.

At present, safety data of this product in clinical use have not been obtained. The clinical safety of MSCs has been supported by a large number of research data. Fever is the most common adverse reaction after MSCs treatment, with the highest incidence of 39% reportedly. Other symptoms such as fatigue could occur as well, which generally could remit spontaneously without treatment. No other adverse reactions related to mesenchymal stem cell therapy were reported.

MSCs-Exo has no immunogenicity due to the absence of MHC-I or MHC-II molecules on its surface. The volume of MSCs-Exo is much smaller than that of MSCs, which can avoid the obstruction and damage of capillaries. Therefore, it can be inferred that the symptoms like fever induced by MSCs-Exo will be significantly less than those of MSCs.

We designed this study to further evaluate the safety of MSCs-Exo in healthy volunteers. Cellular Biomedicine Group Ltd (Shanghai) provides the production and quality control of the research products. MSCs-Exo is secreted by mesenchymal stem cells. The MSCs used for the preparation

of this product comes from the "healthy adult adipose stem cell bank" which meets the ethical requirements. According to the production standard of clinical research preparation, the exosomes secreted by stem cells were obtained by ultrahigh-speed centrifugation and filled aseptically. The stem cell bank has been certified by National Institutes for Food and Drug Control (NIFDC), and the "allogenic adipose mesenchymal stem cell injection" from the bank has been approved by the Center for Drug Evaluation (CDE) (No. CXSL1800109 and CXSL900075). During the whole clinical study process, we will strictly obey the relevant national regulations and ethical requirements.

## **5. Voluntary principles**

1. You choose to participate in this study voluntarily.
2. If you agree to participate in this study, you must sign the informed consent. During the course of the study, you have the right to withdraw at any time without any reason, and it will not affect the other treatment for you.
3. If you take part in this study, we sincerely recommend that you complete all procedures and follow-up under the doctor's guidance for the systematic and complete evaluation.

## **6. Study process**

24 eligible volunteers are expected to be enrolled in this study. The whole research process includes screening, aerosol inhalation, observation, and

follow-up periods, which last for about 7 days. If you agree to participate in this study, you should first sign the informed consent.

#### (1) Screening period

Before being enrolled in the study, you should first accept the relevant screening examination. This stage is the screening period. The doctor will ask and record your basic information and past medical history, measure vital signs, conduct a physical examination, infectious disease detection, blood routine, urine routine, blood biochemistry, coagulation function, immunology, blood pregnancy (female volunteers), electrocardiogram, and any necessary tests. Qualified subjects are enrolled in the study.

#### (2) Aerosol inhalation period

In this study, five nebulization dose groups are set up. Three volunteers are included in groups 1 and 2, and 6 volunteers are included in groups 3, 4, and 5. The subjects who enter the study are numbered in the order in which they enter the study (E001-E024). Subjects E001-003, E004-006, E007-012, E013-018, and E019-024 received initial dose, twice the initial dose, 4-fold dose, 6-fold dose, and 8-fold dose, respectively. Every subject is assigned to receive only one dose.

Before receiving aerosol inhalation, every subject is admitted to the respiratory daily care ward of the respiratory and critical care medicine department of Ruijin Hospital. The skin test of MSCs-Exo is performed firstly. After passing the skin test, the subjects receive aerosol inhalation.

The nebulization time is 30 minutes, and the patients are observed in the hospital until 24 hours after the nebulization.

## **7. Risks and adverse reactions**

In this study, mild fever and allergies associated with the study product are expected after nebulization which could be controlled by routine medical treatment. If you suffer any adverse reactions during this study, the doctor will go to any lengths to treat you. Please actively cooperate with the doctor and receive corresponding symptomatic treatment.

## **8. Benefits and Compensation**

The following benefits are available to subjects:

During the study, you will receive the relevant tests free of charge. According to the test results, the doctor could know about your physical condition more completely and systematically, and provide you with necessary health advice and guidance. Your contribution to the medical cause will be very meaningful.

Subjects who participate in the study will receive the following compensation:

- (1) Those who complete the screening test can get 500 yuan.
- (2) After being screened and accepting the nebulization operation, 2000 yuan will be given.
- (3) Those who are qualified to enter the study, accept nebulization operation, and complete the relevant examination on the second day, will

get 3000 yuan in total.

(4) Subject who completes all the procedures will get 4000 yuan in total.

(5) The above compensation is after-tax income.

## **9. Subject responsibilities**

As a subject, you have the following responsibilities:

(1) It is necessary to provide detailed information about your past medical history and current physical condition.

(2) The doctor should be informed of any symptoms and other drugs except the products used in the clinical study.

(3) During the study, your doctor will inform you which drugs can and cannot be taken during the study. Consult your doctor before taking any new medications.

(4) During the whole study period, you are not allowed to participate in any other clinical trials or studies on drugs or medical devices.

## **10. Instructions for women of childbearing age**

This study did not include female subjects during their pregnancy and lactation period.

Female subjects with fertility (including women of childbearing age and those with menopause less than 1 year) need to take effective contraceptive measures during the whole research process, from the beginning of the study to 3 months after the end of the trial.

The effective contraceptive methods required in this study include:



Implant IDU or IUD for contraception.

Use a condom or uterine cap for barrier contraception.

## **11. Privacy**

If you decide to participate in this study, your participation and your personal information in the study are confidential. You will not be identified, and any information that can identify you will not be disclosed to members outside the research team unless your permission is obtained. All research members and research sponsors are required to keep your identity confidential. Your files will be kept in a locked file cabinet for researchers' reference only. In order to ensure that the study is carried out following the regulations, if necessary, members of the Government Administrative Departments or the Institutional Review Board (IRB) may access your personal data in the research unit as required. No personal information will be disclosed when the results of this study are published.

## **12. Research costs**

### **(1) Clinical study products and related examination costs**

The products, tests, and operations related to this study are free of charge.

### **(2) Compensation for injury of subjects**

We will take the following measures to deal with the injury of the subjects during the study:

1) Before the start of this study, we purchase the corresponding clinical study insurance for all participants.

2) We will provide active and free treatment for the injury directly caused by this study. The subjects should actively cooperate and receive treatment.

3) The cost of treatment for adverse events related to the study products that occur during the study will be paid by the clinical study insurance.

### **Ethical Approvement**

The study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

### **Contact**

You can keep tracking the information and research advances related to this study. If you have any problems related to this study, or have any discomfort or injury during the course of this study, or have questions about the participant's rights and interests in this study, you could contact Dr. Shi at +8615800590157.

Besides, you could contact the ethics committee at 86-021-54661789 for more information on the informed consent process, the subject's rights, and the injury and discomfort you suffer in the study.